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10/594,864	11/30/2006	Takashi Shinohara	701067	1275

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EXAMINER
SGAGIAS, MAGDALENE K

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,864	SHINOHARA ET AL.	
	Examiner	Art Unit	
	MAGDALENE K. SGAGIAS	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *17-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/11/07;1/2/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-34 are pending.

Applicant's election with traverse of group I, claims 1-16 in the reply filed on 2/22/08 is acknowledged. The traversal is on the ground(s) that although the Office cites to Nagano et al. (Biology of Reproduction, 68:2207-2214 (2003)) as evidence that the special technical feature is known in the art, Nagano et al. only discloses a method of expanding spermatogonial stem cells and does not disclose the production of pluripotent stem cells, as required by the pending claims. Applicants argue that spermatogonial stem cells and pluripotent stem cells derived from testis cells differ substantially in their properties (see, e.g., page 25, lines 22-32, and page 28, line 31, through page 32, line 9, of the specification). This is not found persuasive because the art teaches that spermatogonial stem cells derived from the gonadal ridge cell lineage determination during embryogenesis and generation of pluripotent embryonic stem cells, the three primary germ layers form during normal development (path 1). 1) embryonic stem cells from the inner cell mass (path 2) or embryonic germ cells from the gonadal ridge (path 3) can be cultured and manipulated to generate cells of all three lineages (see Neuringer et al, (Respiratory Research, 5-6: 1-9, 2004, figure 1, page 2).

The requirement is still deemed proper and is therefore made FINAL.

Claims 17-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/22/07.

Claims 1-16 are under consideration.

Specification

The amendment to the specification filed on 9/29/06 has not been entered. The paragraph provided as a replacement paragraph, directed to page 56, line 1 of the specification, does not match the paragraph located at page 56, line 1 of the specification. Accordingly, the amendment is not directed to the appropriate location in the specification and has not been entered. .

Applicants failed to provide an English translation of the foreign application JAPAN P. 2004-101320 03/30/2004.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by **Nagano et al,** [Biology of Reproduction, 68: 2207-2214, 2003 (IDS)].

Nagano et al, teach culturing testis cells from transgenic mice which express lacZ in all cell types including all types of postnatal male germ cells using a medium containing glial derived neurotrophic factor (GDNF) to obtain pluripotent stem cells (figure 3, p 2208, 1st column under Materials and Methods) (claim 1).

Nagano et al teach the medium further contains leukemia inhibitory factor (LIF), basic fibroblast growth factor (bFGF) and feeder cells (p 2208, 1st column under Materials and Methods) (claims 2-4).

Nagano teaches the testis cells are spermatogonial stem cells, wherein the spermatogonial stem cells are germ cells (whole document) (claims 5-6).

Thus, Nagano et al anticipate the claimed invention.

Claims 8-11 are rejected under 35 U.S.C. 102(a) as being anticipated by **Kubota et al,** (PNSA, 101(47): 16489-16494, 2004).

Kubota et al, teach testis cells enriched for spermatogonial stem cells (SSCs) were prepared from pups from the hemizygous transgenic mice, DBA/2J X ROSA, or C57BL/6 X ROSA, or C57GFP X ROSA by magnetic-activated cell sorting (MACS) with magnetic microbeads conjugated to anti-Thy-1 antibody (p 16490, 1st column, 1st paragraph and under cell culture section). Kubota teaches the enriched SSCs were cultured on STO feeders in wells of culture plates (p 16490, under cell culture). Kubota teaches human GDNF human bFGF, rat GFR□1-Fc were used in the culture medium and in addition of LIF or EGF was also added in the culture medium (p 16490, 1st column; p 16493, 1st column, 1st paragraph). Kubota teaches the cells were subculture at 5- to 7-day intervals and the medium was changed every 2-3 days (p 16490, 2nd paragraph, last six sentences) limitations of step 1 and step 2 of claims 8 and 12 (claims 8-11).

Kubota teaches the testis is derived from a mammal (claim 13).

Kubota teaches the mouse is postnatal (p 16491, 2ne column, 1st paragraph) (claim 14).

Kubota teaches said cells express a6-intefgrin and are negative for c-kit (p 16493, 1st column, 1st paragraph) (claims 15-16).

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See *In re Ludtke* 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. I*n re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972) and In re Fitzgerald, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34(CCPA 1977)).

There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003).

“Products of identical chemical composition can not have mutually exclusive properties.” A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Applicant is referred to MPEP 2112 for further discussion on inherency.

Thus, Kubota anticipates the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an in vitro method for producing mouse stem cells, which comprises culturing a) neonatal mouse seminiferous tubule, wherein removal of the non-adherent cells results in established colonies expressing SSEA-1, Forsman antigen , β1-integrin, α6-integrin, EpCAM, CD9, EE2 and c-kit markers and b) culturing adult mouse testis selected for the CD9 marker results in established colonies expressing SSEA-1, Forsman antigen , β1-integrin, α6-integrin, EpCAM, CD9, EE2 and c-kit markers, using a medium containing glial cell derived neurotrophic factor (GDNF), leukemia inhibitory factor (LIF), basic fibroblast growth factor (bFGF), , does not reasonably provide enablement for producing pluripotent stem cells to any other animal species. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to producing pluripotent stem cells, which comprises culturing testis cells using medium containing GDNF or equivalent thereto to obtain pluripotent stem cells, LIF, bFGF, feeder cells and the testis cells are p53-defficient.

The claims are broad in scope, encompassing a method that would embrace maintaining pluripotency of any species or human pluripotent cells by culturing testis cells using a medium containing GDNF, LIF, bFGF, feeder cells and the testis cells are p53-deficient. The disclosure provided by the applicant, in view of the prior art, must encompass a wide area of knowledge to a reasonably comprehensive extent. In other word each of those, aspect considered broad must be shown to reasonable extent so that one of the ordinary skills in the art at the time of the

invention by applicant would be able to practice the invention without any undue burden being on such artisan.

The specification teaches testis cells were collected from newborn (0-8 days old) ddY mice, DBA/2 mice or transgenic mouse line C57BL6/Tg14 (act-EGFP-Osby01) that was bred into DBA/2 background (designated Green) [0206]. Because these Green mice have the expressed the EGFP gene in substantially all cell types, it is possible to track the cells derived from the mice can be tracked with the fluorescence of EGFP as the indicator [0206]. The specification also teaches for some experiments, testis cells were collected from a newborn p53 deficient mouse in ICR background (Oncogene, vol. 8, p 3313-3322, 1993) [0207]. The specification teaches for some experiments, testis cells were collected from a newborn p53 deficient mouse in ICR background [0207]. The specification contemplates the pluripotent stem cells obtained by the production method of the present invention have the capability of differentiating into all somatic cells constituting a living organism; all experimental techniques and methods applicable to ES cells or EG cells can be applied to the pluripotent stem cells; using the pluripotent stem cells, it is possible to produce diverse functional cells, tissues, animals (excluding humans) and the like [0186]. The specification further contemplates that pluripotent stem cells genetically modified it is possible to produce genetically modified diverse functional cells, tissues, animals (excluding humans) and the like [0186]. While the specification teaches that the cultured mouse testis cells exhibit the claimed cell surface markers, however, the specification fails to provide guidance for producing pluripotent stem cells by forming the three somatic lineages that is by forming endoderm cells, ectoderm cells and mesoderm cells. **Brinster** (Science, 316: 404-405) notes GDNF appears to be a primary regulator of the self-renewal versus differentiation fate decision for mouse and rat SSCs (7, 14), and it is probably a conserved self-renewal signal for all mammalian SSCs and similar to embryonic stem cells

(ESCs), SSCs grow in vitro on feeder cells in islands or clumps, and they stain positive for POU domain transcription factor 1 (Oct 3/4) and alkaline phosphatase (p 404, 3rd column). However, Brinster also notes that even these observations suggested that SSCs might be pluripotent, however, whereas ESCs readily generate teratocarcinomas when transplanted in vivo, SSCs do not form tumors under similar conditions and whether the normal adult SSC can be induced to become pluripotent remains controversial. **Turnpenny et al,** (Stem Cells, 24: 212-220, 2006) note the influence of the basic media and feeder layers, all groups reporting hEGC derivation and culture have included other additives and their use originates from mouse pluripotent stem cell derivation and culture however, definitive requirements for any in equivalent hEGC cultures have yet to be established conclusively (p 215, 1st column, under media additives and critical factors). Moreover, Turnpenny et al note there are differences in pluripotent stem cells between mice and humans and despite activation of the LIFR/gp130-STAT3B pathway, LIF (administered in human recombinant form) does not maintain self-renewal of hESCs, which require feeder cells or their conditioned media with an extracellular matrix (p 215, 2nd column, last paragraph). Turnpenny et al note several groups have noted difficulty in maintaining hEGCs undifferentiated long-term and this problem of undifferentiated status contrasts with other pluripotent stem cell types: hESCs and human embryonal carcinoma cells (hECCs) and mESCs and mEGCs, all of which have been more extensively characterized (p 217, 1st column, 1st paragraph). hEGC cultures have proliferated extensively; however, the proportion of cells expressing pluripotent markers (e.g., OCT4 and stage specific embryonic antigen [SSEA] family members declines over time, variably from 2 to 3 months onwards, and is exacerbated by freeze-thaw routines (p 217, 1st column, 1st paragraph).

The claims embrace the culture of testis cells for the production of pluripotent stem cells from a mouse, human and other species. The specification exemplifies the culture of mouse

seminiferous tubule cells expressing CD9 epitope for the production of stem cells. However, the specification has not provided guidance for the production of pluripotent stem cells from fully differentiated epithelial cells or fibroblasts contained in the culturing testis cells as embraced in the instant claims. The specification has not provided guidance for the production of pluripotent stem cells from fully differentiated cells, wherein the pluripotent stem cells are able to induce all three germ layers. The specification has not provided guidance for the production of pluripotent cells from the testis cell of all species. The art teaches that LIF is not required to maintain self-renewal of human ES cells, while it is critical for the maintenance of mouse ES cells (Ginis et al, 15;269(2):360-80, 2004) (p 373, 1st column, 2nd paragraph). Verfaile et al (Hematology, 31: 369-391, 2002) teach that in somatic cells the capacity of telomere repair pathways appears to be limiting and telomere shortening effectively limits the proliferative potential of such cells (p 374, 1st column, last paragraph). Verfaile et al teach the mouse and human ES cells differ in their growth properties and while mouse ES cells grow in attached rounded masses in which single cells are difficult to identify, the primate cells grow in flat colonies with distinct cell borders in monolayer culture (p 377, 1st column, last paragraph). Moreover, Verfaile et al teach a series of surface antigens characterize primate pluripotent stem cells and the stage-specific embryonic antigens (SSEA) 1, 3, and 4 are globoseries glycolipids recognized by monoclonal antibodies originally raised to distinguish early stages of mouse development (p 377, 1st column, last paragraph). Primate pluripotent cells express SSEA-3 and SSEA-4, expressing SSEA-1 only upon differentiation (p 377, 1st column, last paragraph). Essentially the reverse is true of mouse ES cells (p 377, 1st column, last paragraph).

In light of the above, the state of the art is suggesting that producing pluripotent stem cells from testis from all species might be feasible in the future. The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of maintaining pluripotency of stem cells from testis by forming all three somatic cells

lineages in any animal species or human raised by the state of the art. Therefore, the skilled artisan would conclude that the state of art of producing pluripotent stem cells fro testis is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for producing pluripotent stem cells from testis from all animal species without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for producing pluripotent stem cells by culturing testis in GDNF, LIF, bFGF, and feeder cells by forming the three somatic lineages, and particularly derived from all animal species, the lack of direction or guidance provided by the specification for producing pluripotent stem cells by culturing testis in GDNF, LIF, bFGF, and feeder cells by forming the three somatic lineages, and particularly derived from all animal species, the absence of working examples that correlate for producing pluripotent stem cells by culturing testis in GDNF, LIF, bFGF, and feeder cells by forming the three somatic lineages, and particularly derived from all animal species, the unpredictable state of the art with respect to producing pluripotent stem cells by culturing testis in GDNF, LIF, bFGF, and feeder cells by forming the three somatic lineages, and particularly derived from all animal species, the undeveloped state of the art pertaining to producing pluripotent stem cells by culturing testis in GDNF, LIF, bFGF, and feeder cells by forming the three somatic lineages, and particularly derived from all animal species, and the breadth of the claims directed to all animal species, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 12 of copending Application No. 10/553,118. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods in both claims overlap in scope of having culturing the cells under GDNF, LIF and feeder cells.

For example, claim 1 of the instant invention is directed to a method for producing a pluripotent stem cells, which comprises culturing testis cells using a medium containing GDNF. Claims 2-6 are directed to wherein the medium contains LIF, bFGF and feeder cells and wherein the testis cells are spermatogonial stem cells. Whereas, claim 1 of the U.S. Patent No. US 10/552,118 is directed to a method for growing spermatogonial stem cells, which comprises growing spermatogonial stem cells by culturing the spermatogonial stem cells using a medium containing GDNF and LIF. Thus, the claims of the US 10/553,118 differ only with respect to the order of adding GDNF and LIF in the culture medium. As such, they are obvious variants of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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